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A STUDY OF THE ACTION OF ANTISTREPTOCOCCUS SERUM IN STREPTOCOCCUS INFECTIONS IN MAN.*

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In our earlier study of antistreptococcus serum[1] we found that the blood serum of persons with streptococcus infections, although it might be deficient in streptococcus opsonin, was still able to activate antistreptococcus horse serum. From this we inferred that antistreptococcus serum would probably have immunizing and curative action against living streptococci in man. The present report has to do with some studies of phenomena arising after injections of antistreptococcus serum in patients infected with streptococci. We have not undertaken the treatment of a large number of cases so as to arrive at results by statistics. Our purpose has been to determine whether in patients with streptococcus infections, injections of antistreptococcus serum were followed by an appreciable increase of antistreptococcus bodies in the blood, and if so, whether coincident clinical improvement was apparent. Since streptococcus infections in man run such variable courses and so large a proportion terminate in spontaneous cure, it has been difficult to arrive at definite conclusions as to the real therapeutic value of antistreptococcus serums. Some clinical observers have been enthusiastic as to the results obtained while others have only met with disappointment. We have hoped that the present study might aid in clearing up some of this uncertainty. If the administration of the serum should be followed simultaneously by an increase in antistreptococcus bodies in the blood and by an amelioration of the symptoms of disease, it would be natural to infer that both were brought about by the action of the serum. It must, however, be remembered that in the treated cases we have a combination of a passive immunity produced by the injected antibodies and of an active immunity due to the action of the infecting bacteria.

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* Received for publication April 10, 1912.

[1] *Jour. Infect. Dis.*, 1911, 9, p. 130.

In our former studies in guinea-pigs we found that the increase of opsonin in the blood after injections of antistreptococcus serum was a fairly accurate guide to the protection afforded. In the cases here reported we have studied the variations in streptococcus opsonin and also the phagocytic activity of the leukocytes subsequent to injections of antistreptococcus serum. Erysipelas and scarlet fever were selected as being the diseases of which a sufficient number of cases were available so that very severe examples might be chosen. A modified Wright's technic for determining the opsonin was followed, using a streptococcus culture which had lost much of its virulence under cultivation. The antistreptococcus serum employed was of two lots of polyvalent serum, kindly furnished for the purpose by Dr. E. M. Houghton, director of the Biological and Research Department of Parke, Davis & Co., to whom we acknowledge our obligation. Before using, the activity of the serums was determined in two ways. One part of the serum was added to nine parts of fresh, normal human serum. Such mixtures when diluted from 48 to 96 times with salt solution opsonized streptococci more than did similar dilutions of corresponding mixtures of normal serums. Also, 1 c.c. of the serums protected guinea-pigs against a fatal dose of living streptococci given 18 hours subsequently.

Early in our study we were fortunate in an opportunity of observing the effects of injections of antistreptococcus serum in a woman in whom it was desirable to produce a streptococcus immunity before the performance of an operation for removal of a hypophyseal tumor by the nasal route, since erysipelas seems very apt to follow such operations. The case was in the charge of Dr. Allen B. Kanavel, to whom we are indebted for the privilege of making these observations. Fifty c.c. of antistreptococcus serum were injected the day before and two days subsequent to the operation. Chart 1[1] shows the course taken by the streptococcus index and by the activity of the leukocytes toward streptococci.

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[1] In connection with all the charts in this article "opsonic index" is used to indicate the streptococcus opsonic power of the patient's serum compared with that of normal serum; "cytophagic index" is used to indicate the phagocytic power of the patient's leukocytes with respect to streptococci compared to that of normal leukocytes under the influence of normal serum. The temperature curve is constructed from the highest temperature for each day.

Similar to what is observed in guinea-pigs, there was a rise in the opsonic index and in the activity of the leukocytes. Unfortunately, there developed a pneumococcus meningitis which was fatal. It is likely that this may have modified the curves to some degree after the second day. This observation shows that in man, as in guinea-pigs, a marked rise in opsonin follows the injections of antistreptococcus serum.

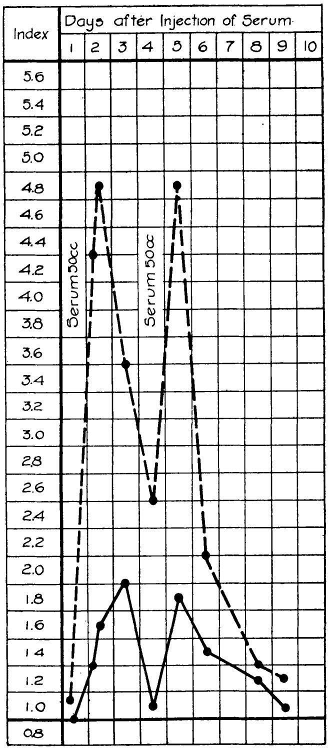

CHART 1.—Showing the opsonic index for streptococci and the increase in the phagocytic power of the leukocytes after the intramuscular injection of antistreptococcus serum in the case of Dr. Kanavel's patient with tumor of the hypophysis.

Solid line = opsonic index.

Broken line = phagocytic power of the leukocytes of the patient as compared with the leukocytes from a normal person (cytophagic index).

Alterations in the streptococcus opsonin and in the phagocytic activity of the leukocytes subsequent to injections of antistreptococcus serum were studied in six cases of erysipelas, two cases of septic scarlet fever and two cases of chronic otitis following scarlet fever. The former eight cases were of a severe type and selected as being likely to run unfavorable courses.

The course taken by the opsonic index, by the phagocytic activity of the leukocytes, and the temperature in the cases of erysipelas which were given the serum and in our uninjected cases is shown in the appended charts (Charts 2 to 7) to which brief clinical notes are added. All of the six cases terminated in recovery, and visible improvement usually began about 24 hours after the serum was given. The improvement was shown by falling temperature, recession of the local swelling, subsidence of delirium, and betterment in the general condition. In short, the impression upon the observers was that recovery was more rapid than could be expected in the usual course of the disease in similar cases. That the rapidly favorable outcome was not accidental was further indicated by the concurrent increase of streptococcus opsonin above that observed in untreated cases. This increase of opsonin was noted at the time when gradual improvement began (Charts 3 and 4) or was sometimes delayed a short time or rose very slowly at first, as if the index rose only when the infection was effectually checked (Charts 5 and 6).

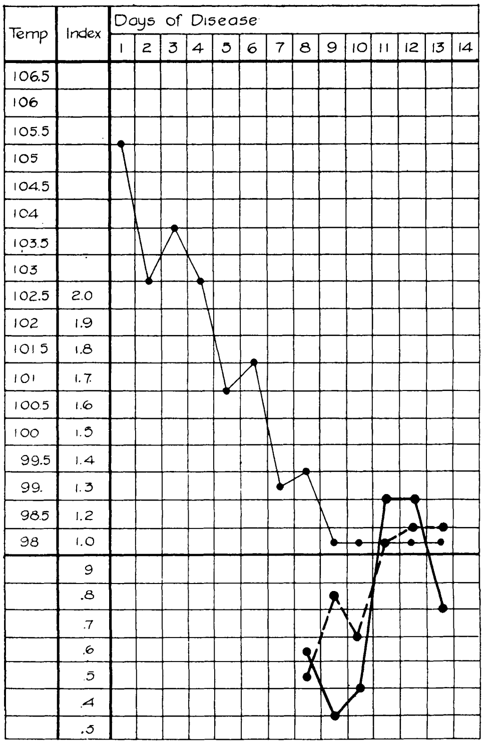

CHART 2.—Severe erysipelas, no serum, recovery. Case 1.
Heavy solid line = opsonic index.
Heavy broken line = phagocytic power of patient's leukocytes as compared with that of normal leukocytes (cytophagic index).
Fine solid line = temperature.

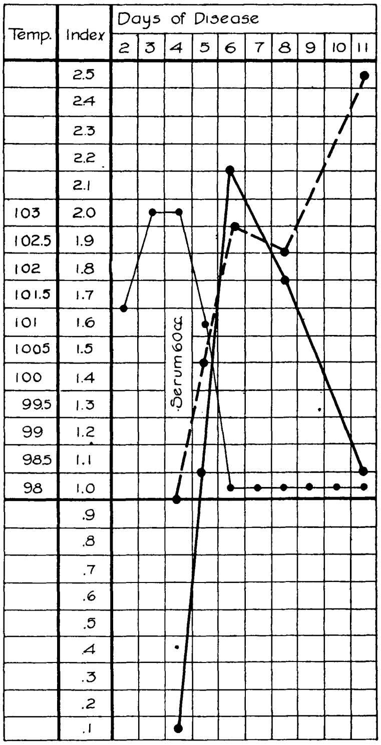

CHART 3.—Severe erysipelas, injection of serum on the fourth day, recovery. Case 2.
Heavy solid line = opsonic index.
Heavy broken line = phagocytic power of patient's leukocytes as compared with that of normal leukocytes (cytophagic index).
Fine solid line = temperature.

In the case represented by Chart 7, the indexes were not taken before the serum was given. It is likely that the alteration on the day following the injection was brought about by the serum, but the subsequent course corresponds to that noted in untreated cases.

The degree of passive immunity was not sufficient to check the infection and an active immunity was finally developed.

The serum was administered to two cases of septic scarlet fever. In each there was a leukocytosis and in each the leukocytes showed increased phagocytic activity before the injection. In each, the opsonic index was subnormal, but rose after the serum was injected, and with this rise the temperature fell and the general condition improved. Both cases were desperately sick with a very bad outlook before the serum was given, and both made as rapid and complete a recovery as occurs usually in untreated cases of

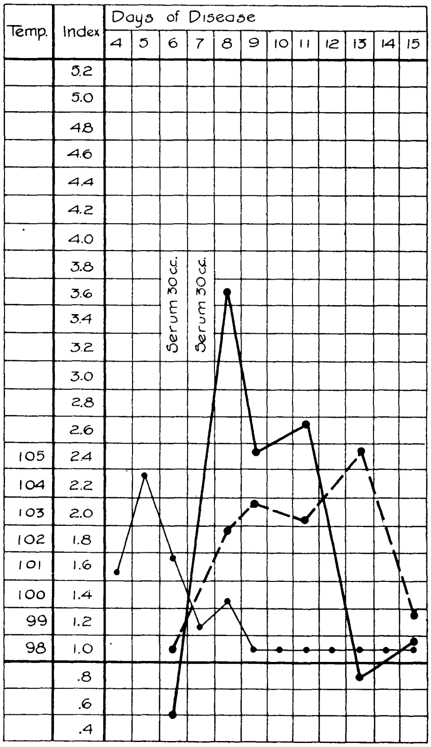

CHART 4.—Severe erysipelas, injection of serum on sixth and seventh days, recovery. Case 3.

Heavy solid line = opsonic index.

Heavy broken line = phagocytic power of patient's leukocytes as compared with that of normal leukocytes (cytophagic index).

Fine solid line = temperature.

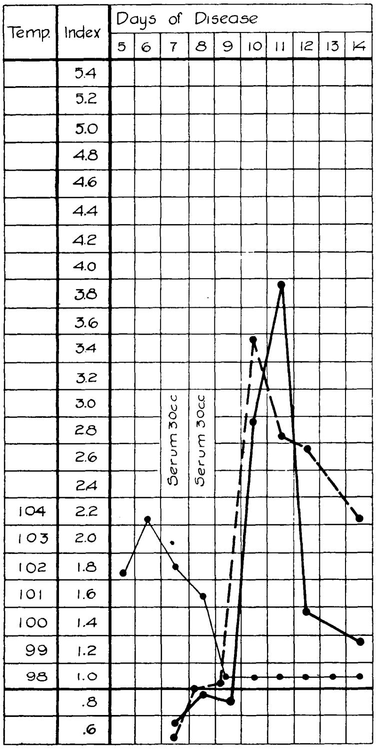

CHART 5.—Severe erysipelas, injection of serum on the seventh and eighth days, recovery. Case 4.

Heavy solid line = opsonic index.

Heavy broken line = phagocytic power of patient's leukocytes as compared with that of normal leukocytes (cytophagic index).

Fine solid line = temperature.

moderate severity. Subjoined are charts of the observations in these cases with brief clinical notes, and also for comparison a similar chart from an uninjected case (Charts 8, 9, 10).

In two cases of chronic suppurative otitis media following scarlet fever in which cultures from deep in the ear yielded streptococci in almost pure growth, a single injection of 60 c.c. was given. Both children had received diphtheria antitoxin several weeks before, and they both developed a severe serum reaction a few hours after the injections. In each case the opsonic and cytophagic indexes rose very considerably and remained elevated several days. The effect upon the aural discharge was not pronounced.

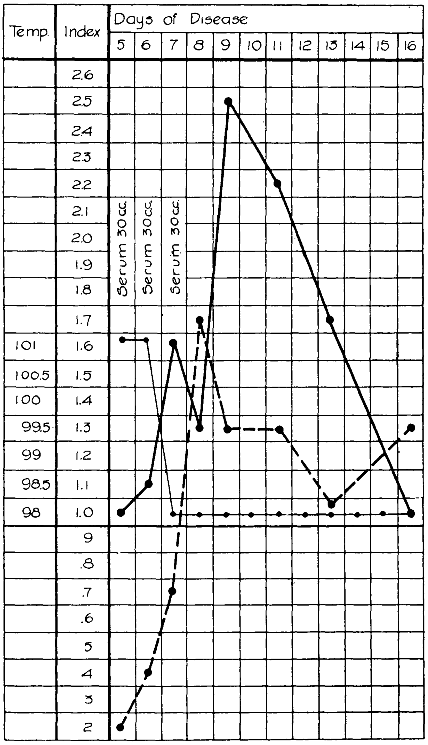

CHART 6.—Severe erysipelas, injection of serum on the fifth, sixth, and seventh days, recovery. Case 5.

Heavy solid line = opsonic index.

Heavy broken line = phagocytic power of patient's leukocytes as compared with that of normal leukocytes (cytophagic index).

Fine solid line = temperature.

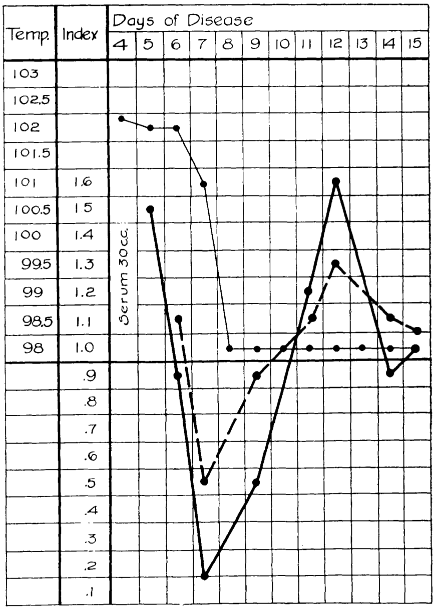

CHART 7.—Severe erysipelas, injection of serum on the fourth day, recovery. Case 6.

Heavy solid line = opsonic index.

Heavy broken line = phagocytic power of patient's leukocytes as compared with that of normal leukocytes (cytophagic index).

Fine solid line = temperature.

We have not found that the injection of serum produces an increase in leukocytes. However, a leukocytosis already present falls after the administration of the serum as symptoms abate (Chart 9).

The increased activity of the leukocytes following the serum injections does not appear to be specific, as we had thought probable in our former study in guinea-pigs.

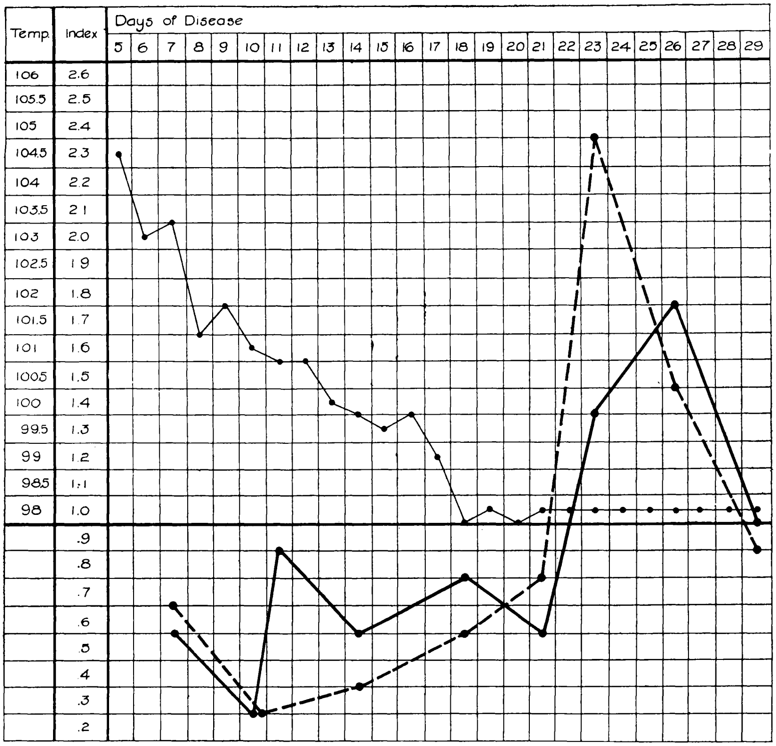

CHART 8.—Septic scarlet fever, no serum, recovery. Case 7.
Heavy solid line = opsonic index.
Heavy broken line = phagocytic power of patient's leukocytes as compared with that of normal leukocytes (cytophagic index).
Fine solid line = temperature.

Most of the injections have been made into the muscles to facilitate rapid absorption. No untoward effects were noted after such injections. In very urgent cases the intravenous injection should be considered as likely to yield the quickest results.

An experiment was made (Tunnicliff) to determine the concentration of streptococcus opsonins in the blood of rabbits following the intravenous, intramuscular, and subcutaneous injections of 4 c.c. of antistreptococcus serum. The opsonic index rose in 10 minutes following the intravenous injection, in two hours after the intramuscular injection, and in 24 hours after the subcutaneous

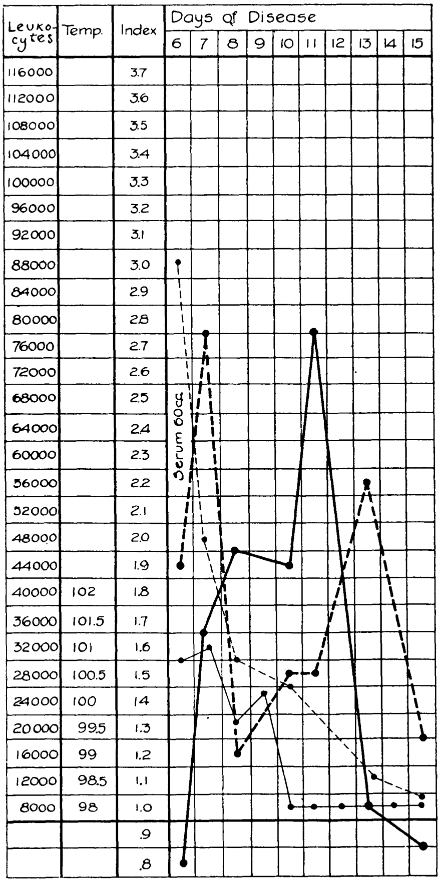

CHART 9.—Septic scarlet fever, injection of serum on the sixth day, recovery. Case 8.

Heavy solid line = opsonic index.

Heavy broken line = phagocytic power of patient's leukocytes as compared with that of normal leukocytes (cytophagic index).

Fine solid line = temperature.

Fine broken line = leukocytes.

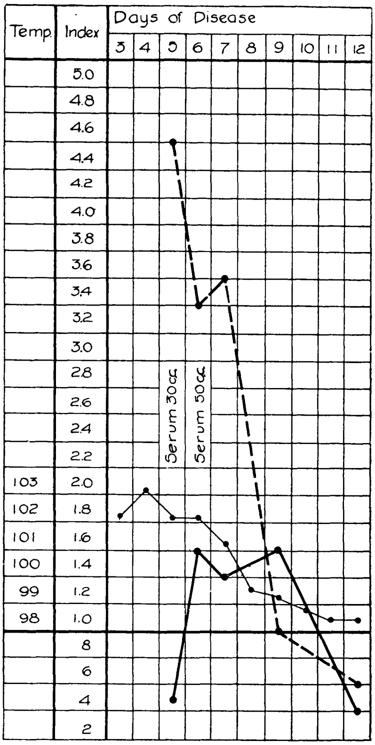

CHART 10.—Streptococcic scarlet fever, injection of serum on fifth and sixth days, recovery. Case 9.

Heavy solid line = opsonic index.

Heavy broken line = phagocytic power of patient's leukocytes as compared with that of normal leukocytes (cytophagic index).

Fine solid line = temperature.

injection. The highest index produced by the intravenous injection was 3.9; by the intramuscular, 2.5; and by the subcutaneous, 1.9. The rise persisted in each case for 24 hours.

The dose of serum may be said to be entirely arbitrary. Our experience corresponds with that of other observers in pointing toward rather large doses as required to produce results. This is also suggested by the relatively large quantities of serum necessary to bring about immunity in experimental animals. As a guide to the amount of serum required by the individual case, the opsonic index appears of value. When a rise of the opsonic index after the injection of serum is promptly followed by a fall below normal, even though associated with some amelioration in the clinical symptoms, it would seem best to give more serum at once. In similar manner a persistent leukocytosis may be found useful as pointing to the need of further administration of serum.

In our former paper we showed that the commercial antistreptococcus serums vary considerably in the amount of antibodies they contain. It is therefore to be expected that they will vary in their effects and that one will accomplish certain results in much smaller doses than another. We also called attention to the fact that the antibodies may be secured in higher concentration by a process of precipitation similar to that employed in the case of antidiphtheric serum. It would be desirable to know whether such concentrated serum would possess higher therapeutic value which might make it possible to administer larger amounts of specific antibodies in smaller bulk.

There is still lacking any definite standardization of antistreptococcus serum, upon which the dosage must be finally dependent. Such standardization would enable the producer to select the horses which yield antibodies in the largest amount.

CASE 1 (Chart 2).—Man, 38 years; on the day of admission erysipelas started in a wound on the back of the neck produced by the surgical removal of a lipoma. The process extended until it involved the entire face, ears, and most of the scalp, reaching a standstill in about a week, followed by uninterrupted recovery.

CASE 2 (Chart 3).—Boy, 6 years; admitted on the second day of illness with typical erysipelas of the entire face, there being extensive blebs on the forehead and one eye entirely closed from swelling of the lids. The border of the area was sharply defined. On the two following days the swelling extended and the general symptoms became more severe. As the temperature fell rapid improvement took place in both local and general condition and he was discharged entirely well 12 days after the onset of the attack.

CASE 3 (Chart 4).—Man, 39 years; attack began four days before admission with swelling on the right side of the face. When admitted there was a well-developed erysipelas of the whole face, one eye being entirely closed; patient nervous, muscles twitching; rapid, general and local improvement came with the fall of the temperature, convalescence being prompt and uncomplicated. Before the first injection the leukocytes were 9,600; before the second injection, 10,200, and 24 hours after, 5,600.

CASE 4 (Chart 5).—Man, 37 years; five days before admission there appeared a swelling of the nose which later extended to one side of the face and then to the other. On admission most of the face was involved in a typical erysipelas with sharply defined borders. On the two following days the swelling extended to the ears and scalp accompanied with much pain and general nervous symptoms; when the serum was injected the patient was actively delirious. The first injection was given at 11:30 P.M. and on the following morning there was no delirium, the temperature had fallen, and general improvement had set in. Recovery was rapid and uninterrupted. Leukocytes before the first injection were 8,400 and before the second injection, 7,100.

CASE 5 (Chart 6).—Man, 38 years; five days before admission the patient pricked a small papule on the lobe of the right ear; three days later the ear was swollen and tender and the swelling extended so that on admission the upper part of the face, including the forehead and both ears, was involved, the eyes being nearly closed. The erysipelas was typical, with sharply defined borders. As the temperature fell the local and general conditions rapidly improved, recovery being prompt and uncomplicated.

CASE 6 (Chart 7).—Man, 45 years; four days before admission chills followed by fever; coincidentally swelling began beside the nose and extended over the entire face and ears with enlargement of the glands behind the right ear. The patient appeared to be in a septic condition. The day after the injection the fever began to fall and both local and general symptoms to improve. The improvement however was slow and recovery took place in about two weeks. In this case the curve of the opsonic index corresponds to that observed in untreated cases, remaining below normal for some days after improvement had commenced and rising above normal only for a short time when convalescence was well established. It would seem that in this case not enough serum was injected to alter the course of the disease appreciably.

CASE 7 (Chart 8).—Man, 17 years; five days before admission he became suddenly sick with intense headache, vomiting, and fever. The next day there was a red rash. On admission he was very sick and delirious, conjunctivae injected, cervical glands enlarged, papillae of the tongue prominent, and diffuse typical rash. There were no diphtheria bacilli in the cultures from the throat. On the tenth day of the disease a purulent discharge from one ear appeared. Improvement came gradually and the recovery was complete.

CASE 8 (Chart 9).—Man, 22 years; severe angina five days before admission, and at about the same time there was noticed an eruption on the skin. When admitted there was a typical scarlatinal rash over the whole body; papillae of the tongue enlarged; mouth and lips very sore; teeth covered with sores; conjunctivae injected; muco-purulent discharge from the inner canthus. The glands and periglandular tissues on the right side of the neck enormously swollen from the clavicle to the lower jaw. Pulse 120. Marked nervous symptoms, the patient being irrational and actively delirious. No diphtheria bacilli in the throat. 60 c.c. antistreptococcus serum injected intramuscularly. On the following day the swelling had extended up on the face, over the angle of the jaw; the patient apathetic and unconscious. Incision into the swollen tissues of the neck yielded only serum. On the next day, two days after the injection of the serum, the patient was resting quietly, was rational, and took food. There was a slight purulent discharge from the incision in the neck. From now on there was rapid and uninterrupted improvement, the wound in the neck closing in 10 days. The discharge from this wound was profuse, the cultures of the pus giving hemolyzing streptococci in pure growths.

CASE 9 (Chart 10).—Man, 18 years; ill several days before admission but the rash had been out only for 24 hours; when admitted there was a general typical scarlet fever eruption and severe angina with a false membrane on one tonsil. No diphtheria bacilli were found on repeated examinations. He was very toxic, irrational, and actively delirious with involuntary evacuations. Ten hours after the first injection he was much better, sleeping quietly, and seemingly improved in every way. From this time improvement progressed rapidly. On the 10th day there appeared acute swelling of the cervical glands which disappeared in a few days without suppuration. Leukocytes before the first injection were 15,600 and before the second injection, 20,600.